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Effect of pitavastatin treatment on changes of plaque volume and composition according to the reduction of high-sensitivity C-reactive protein levels

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ABSTRACT

Background: There are few data regarding the effect of statins on regression and compositional changes of plaque according to the reduction in high-sensitivity C-reactive protein (hs-CRP) levels in acute myocardial infarction (AMI) patients.
Methods: We used serial virtual histology-intravascular ultrasound to assess the efficacy of pitavastatin (dosage: 2 mg/day) on plaque regression and compositional changes according to the degree of reduction in hs-CRP levels from baseline to follow-up [≥1 mg/dl ($n=62$) vs. <1 mg/dl ($n=32$)] in non-intervened non-infarct related artery in AMI patients who were enrolled in the Livalo in acute myocardial infarction study (LAMIS).
Results: Total atheroma and percent atheroma volumes decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl ($-1.7\pm12.4\,mm^3$ vs. $+2.7\pm7.8\,mm^3$, $p<0.015$, and $-0.4\pm3.4\%$ vs. $+0.4\pm4.8\%$, $p<0.001$, respectively). Absolute and %necrotic core volumes decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl ($-0.4\pm3.5\,mm^3$ vs. $+1.9\pm3.4\,mm^3$, $p=0.038$, and $-1.1\pm4.9\%$ vs. $+2.7\pm4.7\%$, $p=0.016$, respectively). Reduction in hs-CRP ≥1 mg/dl at follow-up was the independent predictor of reduction of percent atheroma volume and %necrotic core volume at follow-up [odds ratio (OR), 2.228; 95% confidence interval (CI), 1.390–2.977, $p=0.016$, and OR, 2.204; 95% CI, 1.512–2.916, $p=0.020$, respectively].
Conclusions: Reduction in hs-CRP levels in AMI patients plays an important role in the beneficial effects of statins on the regression and compositional change of coronary plaque.

1. Introduction

Pitavastatin (Livalo®, Kowa, Nagoya, Japan) is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that significantly reduces the levels of plasma low-density lipoprotein cholesterol and modestly increases levels of high-density lipoprotein cholesterol [1]. Statins have a wide range of biologic effects in addition to lipid lowering, including reductions in the levels of C-reactive protein (CRP), a phenomenon commonly termed a "pleiotropic effect" [2–4].

Vascular inflammation plays an important role in atherogenesis and thrombotic events [5]. High-sensitivity (hs)-CRP has been associated with high risk for the development of coronary artery disease [6], and hs-CRP has emerged as a simple tool for detecting

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systemic inflammation in patients with subsequent coronary events [7,8]. Measurement of hs-CRP has been recommended for patients to refine risk assessment [9].

There are limited data regarding the effect of pitavastatin on regression and compositional changes of plaque according to the reduction in hs-CRP levels in acute myocardial infarction (AMI) patients. Therefore, the aim of this study was to assess the efficacy of pitavastatin on plaque regression and compositional changes according to the degree of reduction in hs-CRP levels at follow-up in non-intervened non-infarct related artery in AMI patients who were enrolled in the Livalo® in acute myocardial infarction study (LAMIS).

2. Methods

2.1. Patient population

LAMIS is a substudy of the Korea Acute Myocardial Infarction Registry (KAMIR). The KAMIR is a Korean prospective multicenter online registry designed to reflect the "real-world" practice in Asian patients presenting with AMI including both ST segment elevation MI and non-ST segment elevation MI with support from the Korean Circulation Society since November 2005 [10,11]. Online registry of AMI (at http://www.kamir.or.kr) has been performed at 52 university or community hospitals that are high-volume centers with facilities for primary percutaneous coronary intervention and onsite cardiac surgery. The LAMIS investigators were selected from 10 major percutaneous coronary intervention centers among the 52 KAMIR sites and 1039 consecutive AMI patients who received 2 mg of pitavastatin daily as a sole statin were prospectively enrolled between February 2007 and September 2009. Of these patients, a total of 94 who underwent baseline and follow-up gray-scale intravascular ultrasound (IVUS) and virtual histology (VH)-IVUS for non-intervened non-infarct related artery and checked baseline and follow-up hs-CRP were included in this VH-IVUS substudy. The data were analyzed at quantitative coronary angiography (QCA) and IVUS core laboratory (Chonnam National University Hospital). We divided the patients into two groups according to the degree of the reduction in hs-CRP levels from baseline to follow-up [$\geq$1 mg/dl (n = 62) vs. <1 mg/dl (n = 32)]. The selected value of 1 mg/dl as a classification border of the degree of hs-CRP reduction was determined on the basis of the median change in hs-CRP of 1.01 mg/dl. The presence of ST-segment elevation MI was determined by >30 min of continuous chest pain, a new ST-segment elevation $\geq$2 mm on at least 2 contiguous electrocardiographic leads, and creatine kinase-MB >3 times normal. The presence of non-ST-segment elevation MI was diagnosed by chest pain and a positive cardiac biochemical markers (creatine kinase-MB or cardiac specific troponin-I) without new ST-segment elevation. The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

2.2. Laboratory analysis

Venous blood samples were obtained before IVUS study within 24 h of symptom onset. The blood samples were centrifuged, and serum was removed and stored at −70 °C until the assay could be performed. hs-CRP was assessed by the immunoturbidimetric CRP-Latex (II) hs assay using an Olympus 5431 autoanalyzer (Olympus, Tokyo, Japan). The assay was performed according to the manufacturer's protocol and has been validated against the Dade-Behring method [12]. This assay has a coefficient of variation of ≈5%. Absolute creatine kinase-MB levels were determined by radioimmunoassay (Dade Behring Inc., Miami, FL, USA). Cardiac-specific troponin I levels were measured by a paramagnetic particle, chemiluminescent immunoenzymatic assay (Beckman, Coulter Inc., Fullerton, CA, USA). The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by standard enzymatic methods.

2.3. Angiographic analysis

Coronary angiogram was analyzed with validated QCA system (Phillips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, the Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and reference diameter were measured in diastolic frames from orthogonal projections.

2.4. IVUS imaging and analysis

All gray-scale and VH-IVUS examinations were performed after intracoronary administration of 300 μg nitroglycerin. A 20-MHz, 2.9F IVUS imaging catheter (Eagle Eye, Volcano Corp, Rancho Cordova, CA, USA) was advanced >10 mm beyond the lesion; and automated pullback was performed to a point >10 mm proximal to the lesion at a speed of 0.5 mm/s.

A single operator blinded to the clinical presentation analyzed the IVUS images and measured diseased segment (normal to normal). The same anatomic image slices were analyzed at baseline and at follow-up. By using the axial landmark (i.e. side branch, calcifications, or unusual plaque shapes) and the known pullback speed, identical cross-sectional image slices on serial studies could be identified for comparison. We measured IVUS images spaced precisely 1 mm apart. The leading edges of the external elastic membrane (EEM) and lumen were traced manually using planimetry software (Echoplaque 3.0, INDEC Systems, Santa Clara, CA, USA) in accordance with guidelines for IVUS from the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies [13]. TAV was calculated by summation of atheroma area from each measured image as: TAV = Σ(EEM area − lumen area). The percent atheroma volume (PAV) was determined using the formula: PAV = 100 × [Σ(EEM area − lumen area)/Σ(EEM area)].

VH-IVUS analysis classified the color-coded tissue into four major components: green (fibrotic); yellow-green (fibro-fatty, FF); white (dense calcium); and red (necrotic core, NC) [14,15]. VH-IVUS analysis was reported in absolute amounts and as a percentage of plaque volume.

2.5. Statistical analysis

The statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean value ± 1SD; comparisons were conducted by Student's t-test or the Wilcoxon rank-sum test if normality assumption was violated. Discrete variables were presented as percentages and frequencies; comparisons were conducted by chi-square statistics or Fisher's exact test as appropriate. Pearson correlation was used to evaluate the correlation between change (Δ) of hs-CRP from baseline to follow-up and change of PAV and between change of hs-CRP from baseline to follow-up and %NC volume from baseline to follow-up. Multivariable logistic regression analysis was performed to identify the independent predictors of PAV reduction and %NC volume reduction at follow-up. A p-value <0.05 was considered statistically significant.

Table 1
Baseline characteristics.

	hs-CRP reduction <1 mg/dl (n = 32)	hs-CRP reduction ≥1 mg/dl (n = 62)	p-Value
Age (years)	64 ± 12	63 ± 9	0.5
Male gender	24 (75)	44 (71)	0.7
Clinical presentation			0.5
STEMI	24 (75)	42 (68)	
NSTEMI	8 (25)	20 (32)	
Diabetes mellitus	12 (38)	20 (32)	0.6
Hypertension	22 (69)	42 (68)	0.9
Smoking	18 (56)	30 (48)	0.8
Ejection fraction (%)	47 ± 9	45 ± 8	0.2
Creatine kinase-MB (U/l)	14 ± 36	16 ± 42	0.6
Troponin-I (ng/ml)	5.3 ± 17.7	6.7 ± 35.1	0.6
Creatinine (mg/dl)	0.96 ± 0.40	0.99 ± 0.77	0.8
hs-CRP (mg/dl)	0.20 ± 0.31	2.41 ± 4.32	0.001
Total cholesterol (mg/dl)	170 ± 24	195 ± 41	0.001
Triglyceride (mg/dl)	120 ± 70	161 ± 145	0.036
LDL cholesterol (mg/dl)	111 ± 20	123 ± 33	<0.001
HDL cholesterol (mg/dl)	47 ± 10	44 ± 9	0.13
Apolipoprotein A_1 (mg/dl)	134 ± 20	113 ± 14	<0.001
Apolipoprotein B (mg/dl)	80 ± 18	94 ± 27	0.099
Lipoprotien (a) (mg/dl)	32 ± 27	37 ± 27	0.001

Data are n (%), or mean ± SD. hs-CRP, high-sensitivity C-reactive protein; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

3. Results

3.1. Baseline characteristics

The baseline characteristics are summarized in Table 1. hs-CRP level was 2.41 ± 4.32 mg/dl in patients with reduction in hs-CRP ≥1 mg/dl and 0.20 ± 0.31 mg/dl in patients with reduction in hs-CRP <1 mg/dl. There were no significant differences in clinical presentation and prevalence of diabetes mellitus and hypertension and cardiac enzyme levels between both groups. Baseline total cholesterol, triglyceride, low-density lipoprotein cholesterol, and lipoprotein (a) levels were significantly higher in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl.

3.2. Coronary angiographic and IVUS findings

Coronary angiographic and IVUS findings are summarized in Table 2. There were no significant differences in the target vessel, reference diameter, minimal lumen diameter, and percent diameter stenosis between both groups. There were no significant differences in IVUS lesion length, and TAV and PAV between both groups. Absolute and %NC volumes were significantly greater and %FF volume was significantly smaller in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl.

3.3. Follow-up laboratory and IVUS findings

Follow-up laboratory and IVUS findings are summarized in Table 3. Follow-up duration was 8.1 ± 2.2 months in patients with reduction in hs-CRP ≥1 mg/dl and 8.3 ± 1.7 months in patients with reduction in hs-CRP <1 mg/dl. Follow-up hs-CRP, total cholesterol, triglyceride, apolipoprotein B, and lipoprotein (a) levels were significantly greater in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl. Absolute and %NC volumes were significantly greater and %FF volume was significantly smaller in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl.

Table 2
Coronary angiographic and intravascular ultrasound findings.

	hs-CRP reduction <1 mg/dl (n = 32)	hs-CRP reduction ≥1 mg/dl (n = 62)	p-Value
Target vessel			0.11
Left main	12 (38)	14 (23)	
Left anterior descending	12 (38)	20 (32)	
Left circumflex	4 (13)	6 (10)	
Right	4 (13)	22 (36)	
Reference diameter (mm)	3.27 ± 0.57	3.32 ± 0.56	0.5
Minimal lumen diameter (mm)	1.67 ± 0.63	1.56 ± 0.61	0.4
Percent diameter stenosis (%)	49 ± 10	53 ± 11	0.2
IVUS lesion length (mm)	21 ± 13	24 ± 15	0.4
EEM volume (mm^3)	182 ± 95	196 ± 153	0.6
Lumen volume (mm^3)	94 ± 59	89 ± 63	0.7
Total atheroma volume (mm^3)	88 ± 46	106 ± 92	0.2
Percent atheroma volume (%)	49.1 ± 10.5	51.1 ± 10.2	0.4
Absolute FT volume (mm^3)	41.6 ± 24.5	39.0 ± 44.8	0.8
Absolute FF volume (mm^3)	11.4 ± 7.5	7.4 ± 12.2	0.18
Absolute DC volume (mm^3)	5.6 ± 8.0	5.4 ± 5.0	0.9
Absolute NC volume (mm^3)	6.6 ± 7.1	12.3 ± 12.5	0.024
Relative FT volume (%)	63.8 ± 9.6	60.8 ± 10.5	0.10
Relative FF volume (%)	17.5 ± 8.1	11.5 ± 6.2	0.001
Relative DC volume (%)	8.6 ± 8.1	8.4 ± 6.4	0.9
Relative NC volume (%)	10.1 ± 7.0	19.2 ± 11.0	<0.001

Data are n (%), or mean ± SD. hs-CRP, high-sensitivity C-reactive protein; IVUS, intravascular ultrasound; EEM, external elastic membrane; FT, fibrotic; FF, fibro-fatty; DC, dense calcium; NC, necrotic core.

Table 3
Follow-up laboratory and intravascular ultrasound findings.

	hs-CRP reduction <1 mg/dl (n = 32)	hs-CRP reduction ≥1 mg/dl (n = 62)	p-Value
hs-CRP (mg/dl)	0.19 ± 0.35	0.26 ± 0.36	0.4
Total cholesterol (mg/dl)	134 ± 24	149 ± 26	0.013
Triglyceride (mg/dl)	107 ± 54	148 ± 80	0.015
LDL cholesterol (mg/dl)	80 ± 17	89 ± 22	0.076
HDL cholesterol (mg/dl)	46 ± 13	42 ± 10	0.13
Apoprotein A_1 (mg/dl)	128 ± 24	133 ± 30	0.6
Apoprotein B (mg/dl)	58 ± 10	65 ± 9	0.043
Lipoprotein (a) (mg/dl)	30 ± 19	35 ± 29	0.001
EEM volume (mm^3)	184 ± 92	193 ± 149	0.7
Lumen volume (mm^3)	94 ± 56	91 ± 63	0.9
Total atheroma volume (mm^3)	90 ± 45	102 ± 89	0.4
Percent atheroma volume (%)	49.5 ± 10.8	50.0 ± 9.7	0.8
Absolute FT volume (mm^3)	40.8 ± 20.1	39.1 ± 41.0	0.8
Absolute FF volume (mm^3)	11.3 ± 4.2	8.2 ± 11.5	0.4
Absolute DC volume (mm^3)	5.8 ± 8.1	6.5 ± 8.7	0.2
Absolute NC volume (mm^3)	8.5 ± 11.4	11.9 ± 7.8	0.034
Relative FT volume (%)	61.4 ± 14.1	59.5 ± 12.9	0.9
Relative FF volume (%)	17.0 ± 5.1	12.4 ± 8.1	0.019
Relative DC volume (%)	8.7 ± 8.1	9.9 ± 6.9	0.2
Relative NC volume (%)	12.8 ± 10.4	18.1 ± 11.6	0.016

Data are n (%), or mean ± SD. hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; EEM, external elastic membrane; FT, fibrotic; FF, fibro-fatty; DC, dense calcium; NC, necrotic core.

Table 4
Changes in laboratory findings, intravascular ultrasound findings from baseline to follow-up.

	hs-CRP reduction <1 mg/dl ($n=32$)	hs-CRP reduction ≥1 mg/dl ($n=62$)	p-Value
Δhs-CRP (mg/dl)	−0.01 ± 0.11	−2.68 ± 4.90	0.003
ΔTotal cholesterol (mg/dl)	−38 ± 29	−45 ± 32	0.3
ΔTriglyceride (mg/dl)	−18 ± 33	−33 ± 71	0.11
ΔLDL cholesterol (mg/dl)	−33 ± 22	−34 ± 26	0.9
ΔHDL cholesterol (mg/dl)	−0.8 ± 8.2	−1.9 ± 10.0	0.6
ΔApoprotein A_1 (mg/dl)	−6 ± 8	+17 ± 27	0.001
ΔApoprotein B (mg/dl)	−22 ± 19	−28 ± 17	0.3
ΔLipoprotein (a) (mg/dl)	−2 ± 6	−2 ± 5	0.9
ΔEEM volume (mm^3)	+2.3 ± 8.8	−0.3 ± 14.7	<0.001
ΔLumen volume (mm^3)	−0.4 ± 10.5	+1.5 ± 6.1	0.021
ΔTotal atheroma volume (mm^3)	+2.7 ± 7.8	−1.7 ± 12.4	<0.001
ΔPercent atheroma volume (%)	+0.4 ± 4.8	−0.4 ± 3.4	<0.001
ΔAbsolute FT volume (mm^3)	−0.8 ± 3.1	+0.1 ± 3.4	0.2
ΔAbsolute FF volume (mm^3)	+0.1 ± 3.4	+0.8 ± 3.9	0.15
ΔAbsolute DC volume (mm^3)	+0.2 ± 2.3	+1.1 ± 2.8	0.6
ΔAbsolute NC volume (mm^3)	+1.9 ± 3.4	−0.4 ± 3.5	0.038
ΔRelative FT volume (%)	−2.4 ± 4.2	−1.3 ± 4.6	0.2
ΔRelative FF volume (%)	+0.5 ± 4.5	+0.9 ± 4.2	0.5
ΔRelative DC volume (%)	+0.1 ± 4.5	+1.5 ± 4.2	0.10
ΔRelative NC volume (%)	+2.7 ± 4.7	−1.1 ± 4.9	0.016

Data are n (%), or mean ± SD. hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; EEM, external elastic membrane; FT, fibrotic; FF, fibro-fatty; DC, dense calcium; NC, necrotic core.

3.4. Changes in laboratory and IVUS findings from baseline to follow-up

Changes in laboratory and IVUS findings from baseline to follow-up are summarized in Table 4. The change in hs-CRP level from baseline to follow-up was −2.68 ± 4.90 mg/dl in patients with reduction in hs-CRP ≥1 mg/dl and −0.01 ± 0.11 mg/dl in patients with reduction in hs-CRP <1 mg/dl. TAV and PAV decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl. Absolute and %NC volumes decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl. Change in hs-CRP from baseline to follow-up correlated with change in PAV ($r=0.372$, $p=0.005$) and %NC volume from baseline to follow-up ($r=0.385$, $p=0.002$).

3.5. Independent predictors of reduction in PAV and %NC volume

The following variables were tested to determine the independent predictors of PAV reduction at follow-up (variables with $p<0.1$ in univariable analysis): reduction in hs-CRP ≥1 mg/dl at follow-up, diabetes mellitus, baseline PAV, follow-up low-density lipoprotein cholesterol. Reduction in hs-CRP ≥1 mg/dl at follow-up and follow-up low-density lipoprotein cholesterol were the independent predictors for PAV reduction [odds ratio (OR), 2.228; 95% confidence interval (CI), 1.390–2.977, $p=0.016$, and OR, 1.053; 95% CI, 1.006–1.092, $p=0.035$, respectively].

The following variables were tested to determine the independent predictors of %NC volume reduction at follow-up (variables with $p<0.1$ in univariable analysis): reduction in hs-CRP ≥1 mg/dl at follow-up, diabetes mellitus, baseline PAV, baseline %NC volume. Reduction in hs-CRP ≥1 mg/dl at follow-up and baseline %NC volume were the independent predictors for %NC volume reduction at follow-up (OR, 2.204; 95% CI, 1.512–2.916, $p=0.020$, and OR, 1.068; 95% CI, 1.011–1.120, $p=0.033$, respectively).

4. Discussion

The present VH-IVUS study demonstrated that (1) absolute and %NC volumes were significantly greater in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP ≥1 mg/dl, (2) plaque volume decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl, (3) NC component decreased more significantly in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl. The plaque regression and compositional changes (decrease of NC) by usual dose of pitavastatin treatment were more significantly observed in patients with reduction in hs-CRP ≥1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl in AMI patients.

CRP has emerged as a simple tool for detecting systemic inflammation [7,8]. An elevated CRP level is associated with an increased risk of future fatal or nonfatal ischemic complications in acute coronary syndrome patients [16–21]. A previous study demonstrated that CRP was strongly associated with atherosclerosis measured at various sites in the arterial tree [22]. Several mechanisms have been described by which CRP and other inflammatory mediators may be actively involved in atherogenesis [23]. CRP is produced by smooth muscle cells of atherosclerotic lesions [24], and the locally produced CRP could directly participate in atherogenesis and the development of cardiovascular complications.

Several IVUS studies have demonstrated the benefits of statin therapy to be involved in regression or no progression of coronary plaque size [25,2,26]. Recently, the beneficial effects of pitavastatin on plaque regression or stabilization have been reported [27,28]. The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study [27] randomly assigned patients to receive either 4 mg/day of pitavastatin or 20 mg/day of atorvastatin and resulted in significant regression of coronary plaque volume in both pitavastatin and atorvastatin groups. Kodama et al. [28] assessed coronary plaque regression and stabilization following 52 weeks of pitavastatin treatment (2 mg/day) and showed that fixed-dose pitavastatin stabilized vulnerable coronary plaques by the reduction of yellow grade without significant reduction of plaque volume. Another issue is the different effects on plaque progression using high doses of different statins. The Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin vs. AtorvastatiN (SATURN) [29] randomized patients to receive rosuvastatin 40 mg or atorvastatin 80 mg for 24 months and it will determine whether high-dose statins have different effects on plaque progression.

However, conventional gray-scale IVUS has limitations in assessing plaque components. Recently, VH-IVUS, integrated backscatter-IVUS, and iMap-IVUS with radiofrequency 40 MHz IVUS imaging systems have been used for tissue characterization [30,31]. VH-IVUS has the potential to provide detailed qualitative and quantitative information and it can identify four specific plaque components. Plaque components may play a role in the plaque disruption and thrombosis that leads to acute coronary events [32–35]. Lesions with a large lipid core may have a higher risk for disruption than sclerotic plaques [35–37]. Previous studies have demonstrated that statin treatment might result in changes of plaque composition (significant reduction in NC volume and increase in FF plaque volume) by VH-IVUS analysis as well as reduction in plaque volume by gray-scale IVUS analysis [38]. Recently, Hattori et al. [39] reported that 4 mg of pitavastatin treatment induced favorable plaque morphologic changes with an increase in fibrous cap thickness, and decreases in both percentage plaque and lipid volume indexes assessed by serial optical coherence tomography, grayscale, and integrated backscatter-IVUS. The hypothesis in the present study was that standard dose of pitavastatin (2 mg/day) could regress and stabilize the plaque effectively and these changes

in the plaque characteristics might be affected by the degree of the reduction of hs-CRP by pitavastatin treatment.

CRP renders oxidized low-density lipoprotein more susceptible to uptake by macrophages, induces the expression of vascular-cell adhesion molecules, stimulates the production of tissue factor, and impairs the production of nitric oxide [40–43]. Previous studies have demonstrated the association between CRP and effect of statin treatment. McMurray et al. [44] reported a significant interaction between hs-CRP and the effect of rosuvastatin for primary endpoint including cardiovascular death, MI, or stroke, whereby rosuvastatin treatment was associated with better outcomes in patients with hs-CRP $\geq$2.0 mg/l. Nissen et al. [45] reported that the decrease in CRP levels was independently and significantly correlated with the rate of progression by intensive statin therapy. In the present study, plaque change (the decrease of plaque volume as well as plaque composition of NC) was observed more significantly in patients with reduction in hs-CRP $\geq$1 mg/dl compared with those with reduction in hs-CRP <1 mg/dl. These results suggest that the reduction in hs-CRP levels especially in AMI patients plays an important role in the beneficial effects of statins on the progression and compositional change of coronary plaque.

5. Study limitations

First, the present study was based on a small sample, thus raising the possibility of selection bias. Second, gray-scale and VH-IVUS were performed at the discretion of the individual operators leading to potential selection bias. Third, there are some problems in 3-dimensional measurements when we use this type of IVUS system especially at severely calcified segment or branch carina. Fourth, heavily calcified plaques may induce an artifact regarding the codification of plaques by VH-IVUS resulting in an increase in NC content. Fifth, the mean follow-up period was only 8 months; longer-term IVUS follow-up data were not collected.

6. Conclusions

The changes in plaque volume and composition (decrease of NC) by usual dose of pitavastatin treatment were observed more significantly in patients with greater reduction in hs-CRP compared with those with lesser reduction in hs-CRP in AMI patients in this LAMIS-IVUS substudy.

Disclosures

None.

Conflicts of interest

There are no potential conflicts to declare.

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